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Award Number:
**W81XWH-04-1-0490**

TITLE:
**Polychlorinated Biphenyls, Organochlorines & PD Risk: A Case Control Study in Alaskan Natives**

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REPORT DATE:
**May 2011**

TYPE OF REPORT:
**Annual**

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: (Check one)

☒ Approved for public release; distribution unlimited

☐ Distribution limited to U.S. Government agencies only; report contains proprietary information

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| **1. REPORT DATE** *(DD-MM-YYYY)* | **2. REPORT TYPE** | **3. DATES COVERED** *(From - To)* |
|---|---|---|
| 01-MAY-2011 | Annual | 01 APR 2010 - 1 APR 2011 |

**4. TITLE AND SUBTITLE**
Polychlorinated Biphenyls, Organochlorines & PD Risk: A Case Control Study in Alaskan Natives

**5a. CONTRACT NUMBER**
W81XWH-04-1-0490

**5b. GRANT NUMBER**

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
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**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**
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**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**
U.S. Army Medical Research
And Material Command
Fort Detrick
Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**
Approved for public release; distribution unlimited

**13. SUPPLEMENTARY NOTES**
None

**14. ABSTRACT**

The intent of this proposal is to conduct a case-control study of Parkinson's disease (PD) among Alaska Natives to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interview, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project is being conducted in two phases. Phase 1 is a developmental period and is complete for study conduct statewide. The specific aspects of the study design were established, detailed protocols were developed, and Institutional Review Board (IRB) approval was obtained. Phase 2, conduct of the case-control study, is now in progress statewide.

**15. SUBJECT TERMS**
Parkinson's disease, Polychlorinated biphenyl, Organochlorine pesticides, Methylmercury, Alaska Natives, Neurodegeneration

| **16. SECURITY CLASSIFICATION OF:** | | | **17. LIMITATION OF ABSTRACT** | **18. NUMBER OF PAGES** | **19a. NAME OF RESPONSIBLE PERSON** |
|---|---|---|---|---|---|
| **a. REPORT** | **b. ABSTRACT** | **c. THIS PAGE** | | | **19b. TELEPHONE NUMBER** *(include area code)* |
| U | U | UU | | 8 | USAMRMC |

**Standard Form 298 (Rev. 8-98)**
**Prescribed by ANSI Std. Z39.18**

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**A. Introduction**

The intent of this proposal is to conduct a case control study of Parkinson's disease (PD) among Alaska Native people to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides, and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interviews, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project is being conducted in two phases. Phase 1 was a developmental period and is complete. The specific aspects of the study design were established, detailed protocols were developed, and the necessary Institutional Review Board (IRB) approvals for the research were obtained. Phase 2, conduct of the case-control study, is now in progress.

**B. Body**

**SCOPE OF WORK - PHASE 1**

**Task 1**: Develop an ascertainment protocol using Indian Health Service (IHS) provider databases as the primary source, and identifying other possible sources of cases.
**Task 2**: Develop methods for identifying matched controls.
Accomplishments:
Approved methods were utilized to identify cases and controls for recruitment at the Alaska Native Medical Center (ANMC) in Anchorage during prior study years. During the past year, similar methods were adapted to ascertain and recruit cases and controls at clinics in the following locations statewide: Juneau, Sitka, Klawok, Metlakatla, Nome, Kotzebue, Barrow, and Dillingham.

**Task 3**: Develop a preliminary proposal for review by Alaska Native leaders. Subsequent detailed versions of the study protocol will be submitted for review in accordance with protocol.
Accomplishments:
The study protocol, data collection instruments, and informed consents were submitted and approved by all necessary regulatory boards (see Task 7) and the Human Research Protection Office (HRPO) Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) for study conduct at ANMC. The approved documents are being utilized to recruit, enroll, and collect data from study participants statewide.

**Task 4**: Establishing appropriate infrastructure and personnel in Alaska. This will include a physician/neurologist, project manager, and local contacts within each tribal group. In addition, preliminary training in epidemiologic research methods may be a necessary part of a feasibility assessment.
Accomplishments:
Dr. Trimble, our local neurologist, has been involved with the project since its inception. In April 2007 we hired an Alaska based project manager, Amy Wiita. Additionally, Monica Korell, who has been with the project since its inception, continues as the senior study manager. All members of the research team completed human subjects training and training in study specific data collection methods. The team members maintain regular contact and collegial working relationships with

representatives of the 12 tribal health organizations, clinic administrators, and health professionals working with the neurology clinics.

**Task 5**: Develop study instruments and a detailed protocol.
Accomplishments:
Drafts were completed during year 2. We developed a study protocol and study instruments for collecting detailed life histories with special focus on dietary, residential and occupational exposures. After receiving approval from institutional review boards, the HRPO ORP USAMRMC requested additional changes to the protocol. Those changes were implemented, resubmitted, and approved. Study activities are being conducted under the current approvals.

**Task 6**: Refining the study protocol and preparing the operations manual.
Accomplishments:
The study protocol was refined and approved for use in Anchorage as well as 8 of 10 regions outside the Anchorage basin. The operations manual was prepared.

**Task 7**: IRB approval of final protocols.
Accomplishments:
IRB approval to recruit in the ANMC in Anchorage was achieved January 16, 2008, and the study was initiated in Anchorage (see Table 1). In September 2009, we submitted the currently approved protocol and participant materials to all 10 regional tribal boards outside of Anchorage. We subsequently met with tribal boards and local clinic staff in order to describe the study hypotheses and protocol, and to answer any questions they might have. Reviews of the currently approved protocol are underway (n = 2) or complete (n = 8) at each of the 10 regional tribal boards outside of Anchorage (Table 3).

**Table 1. Human Subject Approval Status**

| Institution | Review Board | Status |
|---|---|---|
| Parkinson's Institute | Western IRB | Approved |
| Alaska Native Medical Center | AK Area IRB | Approved |
| Pacific Health Research Institute | VA Pacific Islands Health Care System | Approved |
| University of California San Francisco | UCSF Committee on Human Research | Approved |
| USAMRMC | Office of Research Protections | Approved |

**Table 2. Anchorage Service Unit Tribal Health Boards**

| Institution | Review Board | Status |
|---|---|---|
| Alaska Native Medical Center | AK Native Tribal Health Consortium | Approved |
| Alaska Native Medical Center | SouthCentral Foundation | Approved |

**Table 3. Regional Tribal Health Boards (regions outside the Anchorage service unit)**

| Region Served | Review Board | Submission Status | Approval |
|---|---|---|---|
| Kotzbue | Maniilaq Association | Complete | Approved |
| Sitka, Juneau, Klawok | Southeast AK Regional Health Consortium | Complete | Approved |
| Fairbanks | Tanana Chiefs Council | Review pending | pending |
| Nome | Norton Sound Health Corporation | Complete | Approved |
| Bethel | Yukon Kuskokwim Health Corporation | Complete | pending |
| Kodiak | Kodiak Area Native Association | Complete | Approved |
| Dillingham | Bristol Bay Area Health Corporation | Complete | Approved |
| Barrow | Arctic Slope Native Association | Complete | Approved |
| Ketchikan | Ketchikan Indian Community | Complete | Approved |
| Metlakatla | Metlakatla Indian Community | Complete | Approved |

**SCOPE OF WORK - PHASE 2**

Phase 2 was initiated in February 2008.
The goals of this phase are:

**Task1:** Identify approximately 50 cases of PD and 150 age matched participants without PD among the Native population in Alaska. This will be accomplished by working through tribal leaders, local health care providers and local contacts at the IHS to assist with identifying the most efficient and appropriate means of identifying cases and controls. Specifically, we will request assistance with gaining access to the IHS computerized medical record, the IHS hospital discharge data system, and pharmacy databases. These databases will be used to identify individuals with a diagnosis of PD and individuals on PD medications. Potential participants will be contacted by phone and administered a PD screening instrument. Those who agree to participate and who screen positively will be examined by a trained physician who will use standardized instruments for assessing Parkinson's disease (Unified

Parkinson's Disease Rating Scale, Hoehn and Yahr stage, etc.). Participants will be videotaped to allow expert confirmation of diagnosis. Control participants will be selected from the same population and similarly screened.

Accomplished:

Cases: We established a list of 10 International Classification of Disease (ICD-9) codes related to PD. Patient databases at all clinics where approval has been achieved are periodically searched for these codes. The outputs from the searches are compiled by Dr. Trimble to identify and prioritize suspect cases for study enrollment. To date, we have generated a list of 90 cases with a provisional PD diagnosis statewide. Efforts over the past year have focused on statewide case recruitment. In the past 12 months, case enrollment has tripled.

84 cases with a provisional PD diagnosis were screened (initial review of medical record to determine study eligibility)

- 18 Enrollment in progress
- 39 provided informed consent and are enrolled
  - 16 finished all parts of interview
  - 23evaluations / interviews in progress
- 4 refusals
- 19 ineligible
- 4 on hold

Controls: Because control recruitment is linked to case enrollment, over the past 12 months we have targeted case enrollment on a statewide basis. We will focus on identifying and enrolling matched controls statewide during the next 12 months.

50 potential controls screened at ANMC

- 0 Enrollment in progress
- 34 provided informed consent and are enrolled
  - 33 have finished all parts of interview
  - 1 interview in progress
- 2 refusals
- 8 ineligible
- 6 on hold

**Task 2:** Draw blood from cases and controls to measure levels of PCBs, organochlorine pesticides and methyl mercury.

Accomplished:

Ongoing training is conducted to ensure the proper collection, shipment, and processing of blood samples. As we expand to enroll participants statewide, we have established a network of clinic phlebotomists to be on-call for study blood draws. After labeling, the blood samples are shipped overnight to the Parkinson's Institute laboratory for processing and storage. To date, samples from 65 subjects have been collected, shipped, and processed.

**Task 3:** Administer a structured interview to cases and controls to identify information important to the characterization of PCB, organochlorine pesticides and methyl mercury exposure (life time diet, occupation, place of residence, recreational activities) or identifying potential confounders (smoking cigarettes, drinking coffee, alcohol).

Accomplished:
Of the 73 subjects enrolled to date, 48 interviews have been completed and 25 are in-progress.

**Task 4.** Estimate logistic regression models adjusted for age and other potential confounders to determine the odds of PD among those with high levels of PCB , organochlorine pesticides and methyl mercury exposure, individually and in combination, relative to the odds of PD among those with no or low levels of exposure the toxicants.
Accomplished:
Databases have been developed at the Parkinson's Institute, and procedures for data entry and quality control implemented. Data analysis will not be initiated until all data collection is complete.

## C. Key Research Accomplishments

- Held bi-monthly, face-to-face meetings with collaborators in AK to discuss study progress, challenges, and potential refinement to methods of case ascertainment.
- Case ascertainment, review of potential case medical records by Dr. Trimble, enrollment and data collection continued in Anchorage and was expanded to Juneau, Sitka, Klawok, Metlakatla, Nome, Kotzebue, Barrow, and Dillingham. Case enrollment tripled in the past 12 months.
- Diagnostic evaluations and risk factor interviews were expanded from Anchorage to statewide regions including Juneau, Sitka, Klawok, Metlakatla, Nome, Kotzebue, Barrow, and Dillingham.
- Continued in-person presentations and face to face meetings with tribal health organizations, clinic administrators, and health professionals working with the neurology clinics to give study overviews and address concerns and interests unique to each regional clinic. 80% of the tribal board approvals were received and 20% are still being negotiated.
- Requested and received an extension of the project through April 2014.

## D. Reportable Outcomes

We will not have reportable outcomes until all data collection is finished statewide.

## E. Conclusions

Following the completion of subject enrollment, data and sample collection, and analysis, it will be possible to draw relevant scientific conclusions. Based on study progress to date, we are confident that we will successfully meet our PD ascertainment goal of 50 individuals.

## F. References
None

## G. Appendices
None